Brain Cancer and Occupational Exposure to Lead

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A recent report in the literature suggested a link between occupational exposure to lead and brain cancer. To explore the hypothesis, we applied a job-exposure matrix for lead to the occupation and industry codes given on the death certificate of 27,060 brain cancer cases and 108,240 controls who died of non-malignant diseases in 24 US states in 1984–1992. Brain cancer risk increased by probability of exposure to lead among Caucasian men and women with high-level exposure, with a significant twofold excess among Caucasian men with high probability and high level of exposure to lead (odds ratio = 2.1; 95% confidence interval, 1.1–4.0). Risks were also elevated in the low- and medium-probability cells for African-American men with high-level exposure to lead. Trend by intensity level was statistically significant among African-American men (all probabilities combined). Although exposure assessment was based solely on the occupation and industry reported on the death certificate, these results add to other epidemiologic and experimental findings in lending some support to the hypothesis of an association between occupational exposure to lead and brain cancer risk. Analytic studies are warranted to further test this hypothesis.

A nested case-control study of 26 nervous system tumors found a twofold increased risk among workers with blood lead levels (B-Pb) ≥ 1.4 μmol/L (29 μg/dL), compared with workers whose B-Pb did not exceed 0.7 μmol/L (15 μg/dL).[1] Overall, however, epidemiologic evidence of an association between lead exposure and brain cancer risk is scanty. Increases in brain cancer risk among lead workers have been observed in cohort studies of tetraethyl-lead manufacturers,[2] lead smelters,[3,4] and lead-battery manufacturers.[5] However, none of the observed risk increases were significant, because of the insufficient statistical power of these studies, and negative findings have also appeared.[6] A recent meta-analysis of cancer risk after occupational exposure to lead did not consider brain cancer among the possible outcomes.[7] Non-occupational exposure has been poorly investigated: two astrocytoma cases were observed among children with elevated urinary lead levels,[8] and an elevated brain cancer risk was found among children with residential exposure to heavy traffic in times when leaded gasoline was still in use.[9] Experimental support to the hypothesis is provided by studies in rats, which developed gliomas after oral administration of lead acetate or lead subacetate.[10]

To further explore whether occupational exposure to lead increases brain cancer risk, we conducted a case-control study using data from a national surveillance program of occupational diseases developed since 1984 by the National Cancer Insti-

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tute, the National Institute for Occupational Safety and Health, and the National Center for Health Statistics.

Methods

Since 1984, the National Cancer Institute, the National Institute for Occupational Safety and Health, and the National Center for Health Statistics have supported the coding of occupation and industry titles on death certificates from a number of US states according to the 1980 US Census occupation and industry codes.[11] The database is described in detail elsewhere.[12] In brief, it currently consists of a total of 4.5 million death certificates from 24 US states, covering the years 1984–1992. Only one occupation and industry combination is reported for every subject, and no duration of employment is available. Cases were 27,060 subjects (14,655 men and 12,405 women) who died of cancer of the brain (ICD-9 codes 191.0 and 191.9) at age 35 or older. Six hundred ninety-seven men and 609 women were African American. Subjects who were neither Caucasian nor African American were excluded because of small numbers. Four controls per case were selected from among subjects who died of nonmalignant diseases and were frequency-matched to cases by geographic region, race, gender, and 5-year age-group.

To evaluate risk of brain cancer in relation to occupational exposure to lead, we first designed a job-exposure matrix based on the 1980 US Census list of occupations and industries and subsequently applied it to the codes on the death certificates of cases and controls. An estimate of intensity level (none = 0, low = 1, medium = 2, high = 3) and probability (none = 0, low = 1, medium = 2, high = 3) of exposure to lead was developed for each three-digit occupation and industry code. Intensity level of exposure was estimated based upon information from the literature,[13,14] computerized exposure databases (Occupational Safety and Health Administration files, National Institute for Occupational Safety and Health inspections database), unpublished industrial hygiene reports, and personal experience. Subjects with high-level exposure to lead (average B-Pb above 1.4 μmol/L) were typically employed in lead-smelting plants, lead-battery manufacturing, the printing industry, and production and use of lead compounds in the chemical industry. Lead removal from the printing industry started in the 1970s with the introduction of computers. It is likely that most workers in the printing industry who died in 1984–1992 experienced exposure to lead, although death certificates do not report information on year of starting and quitting work or duration. Occupations such as paint manufacturer, metal products manufacturer, plumber, welder, and worker in garages and service stations (average B-Pb levels ranging from 0.9–1.4 μmol/L) were assigned to a medium level of lead exposure. Bus and other public transportation drivers, utility workers, motor vehicle dealers, and the construction industry were among those workers considered to have a low level of exposure to lead (average blood lead levels below 0.9 μmol/L, with potential for occupational exposure to the metal). Exposure to gasoline and motor vehicle exhausts was included because of the use of leaded gasoline up to the late 1970s. The probability index was estimated based on the proportion of exposed workers within a given job title or industry, and the number of occupations or industries with the same 1980 Census code. In addition, occupations were characterized into two groups, depending upon the sources of exposure. If exposure was determined by the occupation itself regardless of industry, final level and probability scores were obtained by squaring the occupational scores. If exposure was determined by both occupation and industry, then the probability of exposure was dependent upon the industry, and the final score of intensity level resulted from multiplying the intensity-level scores of occupation and industry. The final scores of probability and level of exposure were further categorized within four levels (none = 0, low = 1–2, medium = 3–4, high ≥ 6). Cut points were selected a priori, with the highest category defined by a score of 6 to increase the statistical power.

Odds ratios (ORs) were estimated by logistic regression and 95% confidence intervals (95% CI) by the Wald method, using the GMBO program in the Epicure software package.[15] Included in the logistic regression model were age, marital status (never married versus ever married), rural versus urban residence, and socioeconomic status (five categories, based on the Green's score for specific occupations[16]). The statistical significance of the linear trend by increasing intensity and probability of exposure to lead was tested by dividing the regression coefficients of the variables assumed as noncategorical by their standard error to generate a Z statistic. Under the null hypothesis, this test behaves as a normal standard deviate.[17] Two-tailed P values were considered throughout this article.

Results

Average age at death of brain cancer cases was 62.2 ± 12.4 years among men and 65.8 ± 12.9 among women. African Americans had a significantly younger age at death than Caucasians both among men (60.4 ± 12.4 vs 62.5 ± 12.4, $P < 0.05$) and among women (63.6 ± 13.3 vs 65.9 ± 12.9, $P < 0.05$). Risk was significantly reduced among men and women who were never married (men: OR = 0.5, 95% CI = 0.4–0.6; women: OR = 0.7, 95% CI = 0.6–0.8). A significant 20% increase in risk was associated with rural residence, defined as residence in the countryside or in a city with less than 250,000 inhabitants. Risk of brain cancer rose significantly by increasing socioeconomic status (SES) category among men (ORs =

TABLE 1
Number and Proportion of Subjects Exposed to Lead, by Probability and Intensity Level Categories as Identified by the Job-Exposure Matrix, Based on Death Certificates From 24 US States, 1984–1992*

Study Group	Level of Exposure	Probability of Exposure			
		Low	Medium	High	All
Caucasian men	Unexposed				56792 (81.4%)
	Low	2659 (49.6%)	411 (22.9%)	5087 (87.0%)	8157 (11.7%)
	Medium	2128 (39.7%)	1166 (65.1%)	718 (12.3%)	4012 (5.7%)
	High	574 (10.7%)	214 (12.0%)	41 (0.7%)	829 (1.2%)
	All exposed	5361 (7.7%)	1791 (2.6%)	5846 (8.4%)	12998 (19.6%)
African-American men	Unexposed				2762 (79.2%)
	Low	118 (43.1%)	22 (25.3%)	335 (92.5%)	475 (13.6%)
	Medium	106 (38.7%)	49 (56.3%)	27 (7.5%)	182 (5.2%)
	High	50 (18.2%)	16 (18.4%)	—	66 (1.9%)
	All exposed	274 (7.9%)	87 (2.5%)	362 (10.4%)	743 (20.8%)
Caucasian women	Unexposed				57336 (97.2%)
	Low	381 (39.6%)	191 (44.1%)	203 (81.5%)	775 (1.3%)
	Medium	499 (51.9%)	148 (34.2%)	30 (12.0%)	677 (1.2%)
	High	82 (8.5%)	94 (21.7%)	16 (6.5%)	192 (0.3%)
	All exposed	962 (1.6%)	433 (0.7%)	249 (0.4%)	1644 (2.8%)
African-American women	Unexposed				2991 (98.2%)
	Low	17 (42.5%)	—	3 (100%)	475 (13.6%)
	Medium	20 (50%)	11 (100%)	—	182 (5.2%)
	High	3 (7.5%)	—	—	66 (1.9%)
	All exposed	40 (1.3%)	11 (0.4%)	3 (0.1%)	743 (20.8%)

* Proportion of subjects are expressed by level within the single-probability categories over the total number of subjects assigned to the respective probability category. For all probabilities and for all levels combined, proportions are based of the total number of study subjects.

1.0, 1.3, 1.7, 2.1, with the lowest SES as the reference; $P < 0.0001$) and women (ORs = 1.2, 1.2, 1.8, 2.5; $P < 0.001$).

Overall, subjects with any exposure to lead (all probabilities combined) accounted for 18.7% among Caucasian men, 20.2% among African American men, 2.9% among Caucasian women, and 2.0% among African American women. However, the proportion of subjects with high-level exposure (all probabilities combined) ranged from 0.3%–1.9% among the four study groups. The proportion of subjects with high probability of lead exposure (all levels combined) were 8.4%–10.4% among men and 0.1%–0.4% among women (Table 1). When all probabilities and levels of exposure to lead were combined, an increase in brain cancer risk was observed only among African-American men and African-American women (Table 2). When all levels of exposure were combined, brain cancer risk did not increase with increasing probability of exposure to lead in men or women. When all probabilities were combined, a significant upward trend ($P < 0.01$) in brain cancer risk by level of exposure to lead was observed among African-American men, with a significant 80% increase associated with high-level lead exposure. Within categories of probability and level of exposure to lead, risk increased by probability among Caucasian men in the high level of exposure category, although the trend was not statistically significant ($P = 0.16$). Risk also increased significantly by level of exposure in the low probability category for African-American men ($P = 0.01$). Risk for Caucasian men was highest for subjects with high-probability and high-level exposure to lead (OR = 2.1; 95% CI = 1.1–4.0, based on 14 exposed cases), but trends were not significant (by probability in the high intensity, $P = 0.16$; by intensity in the high probability, $P = 0.60$). Very few African-American men had medium or high probability of exposure. Elevated risks were also observed among Caucasian and African-American women, although cells in the medium and high probability of exposure had very small numbers. Among Caucasian men, the matrix identified only the occupational Census code 736 (typesetters and compositors) in the highest probability and level of exposure to lead. Therefore, the risk increase among this group was entirely driven by this occupation. With the aid of job-exposure matrices, constructed for other purposes with the same procedure described in the Methods section for lead, we identified other suspected neuro-oncogenic workplace exposures among this subgroup. Typesetters and compositors were classified as unexposed to solvents and metal dust, and, therefore, risk associated with high-probability and high-level exposure to lead persisted unchanged among the subgroup of Caucasian men unexposed to solvents (OR = 2.1; 95% CI = 1.1–4.0) and metal dust (OR = 2.0; 95% CI = 1.1–3.9). On the other hand, exposure to electromagnetic fields (EMF) was considered to oc-

TABLE 2
Brain Cancer Risk, by Probability and Intensity Level of Occupational Exposure to Lead Among Men, Adjusted by Age, Marital Status, Residence in Urban vs Rural Areas, and Socioeconomic Status (Risks are Shown by Gender and Race)

Intensity of Exposure	Study Group	Probability of Exposure: Low*	Medium	High	All Probabilities*
Low	Caucasian men	530, 1.0 (0.9–1.1)	80, 0.9 (0.7–1.1)	836, 0.9 (0.9–1.0)	1446, 1.0 (0.9–1.0)
	Afr. Am. men	26, 1.1 (0.7–1.8)	6, 1.3 (0.5–3.4)	65, 0.9 (0.7–1.3)	97, 1.0 (0.8–1.3)
	Caucasian women	82, 1.2 (0.9–1.5)	40, 0.9 (0.7–1.3)	44, 1.2 (0.8–1.7)	166, 1.1 (0.9–1.3)
	Afr. Am. women	6, 2.3 (0.8–6.3)	0, — —	1, 2.4 (0.2–26.9)	7, 2.3 (0.9–5.9)
Medium	Caucasian men	421, 1.0 (0.9–1.1)	224, 1.0 (0.8–1.1)	126, 1.0 (0.9–1.3)	771, 1.0 (0.9–1.1)
	Afr. Am. men	28, 1.6 (1.0–2.5)	10, 1.0 (0.5–2.1)	6, 1.2 (0.5–3.1)	44, 1.4 (1.0–1.9)
	Caucasian women	91, 1.0 (0.8–1.3)	27, 1.0 (0.7–1.5)	7, 1.3 (0.6–3.1)	125, 1.0 (0.9–1.3)
	Afr. Am. women	5, 1.4 (0.5–4.0)	2, 1.0 (0.2–4.6)	0, — —	7, 1.3 (0.5–3.0)
High	Caucasian men	106, 1.0 (0.8–1.2)	43, 1.1 (0.8–1.6)	14, 2.1 (1.1–4.0)	163, 1.1 (0.9–1.3)
	Afr. Am. men	14, 1.8 (0.9–3.3)	5, 2.0 (0.7–5.8)	0, — —	19, 1.8 (1.0–3.1)
	Caucasian women	15, 1.1 (0.6–2.0)	20, 1.2 (0.8–2.0)	4, 1.4 (0.4–4.2)	39, 1.2 (0.8–1.7)
	Afr. Am. women	1, 2.0 (0.2–22.6)	0, — —	0, — —	1, 2.0 (0.2–22.5)
All intensity levels	Caucasian men	1057, 1.0 (0.9–1.1)	347, 1.0 (0.8–1.1)	976, 1.0 (0.9–1.0)	2380, 1.0 (0.9–1.0)
	Afr. Am. men	68, 1.4 (1.0–1.9)	21, 1.3 (0.8–2.1)	71, 1.0 (0.7–1.3)	160, 1.2 (0.9–1.5)
	Caucasian women	188, 1.1 (0.9–1.3)	87, 1.0 (0.8–1.3)	55, 1.2 (0.9–1.6)	330, 1.1 (1.0–1.2)
	Afr. Am. women	12, 1.8 (0.9–3.6)	2, 1.0 (0.2–4.6)	1, 2.4 (0.2–27.2)	15, 1.6 (0.9–3.0)

* Test for trend (African Americans [Afr. Am.]), $P < 0.01$.

cur with high probability among these workers because of the introduction of computers in typesetting in the 1970s, therefore being a potential confounder for our results. Unfortunately, we did not have information on year of ceasing work, which would have allowed a partial discrimination of the effects of these two exposures. However, among Caucasian men and African-American men unexposed to lead, brain cancer risk did not increase by probability and level of exposure to EMF (data not shown). Among African-American men, the patterns of risk increase by level of lead exposure (all probabilities combined and low probability alone) persisted after restricting the analysis to subjects unexposed to electromagnetic fields (data not shown). Industries contributing to the excess brain cancer risk associated with potential lead exposure among African-American men included manufacturing of industrial and miscellaneous chemicals; miscellaneous fabricated metal products; paints, varnishes and related products; and other primary metal industries.

Among study subjects with high-level exposure to lead, brain cancer risk increased independently of age at death. The highest risk was always associated with high probability of exposure to lead either in the 35–54–year age group (OR = 2.0), or in the 55–74–year age group (OR = 2.1), or among subjects aged ≥ 75 years (OR = 2.0).Also, we did not observe regional differences in the risk patterns described above (data not shown).

Discussion

The results of this exploratory case-control study support the hypothesis that occupational exposure to lead may be associated with an increase in brain cancer risk. A risk increase was observed mainly among men likely to have been heavily exposed to the metal, which accounted for only a tiny fraction of our study population, ranging from 0.3%–1.9% across the four study groups. On the contrary, probability of exposure at lower-medium levels and over the total study population did not show an association. Our job-exposure matrix appears to have efficiently classified lead exposure among study subjects, as the exposure prevalence was approximately 20% of men for all probabilities and intensities combined. This figure is about half that reported in a fairly industrialized urban area (47% for all lead compounds combined).[18]

Animal studies provide further credence to the hypothesis, as rats fed lead acetate or lead subacetate developed gliomas.[10] Inorganic and organic lead cross the blood-brain barrier, causing well-known neurologic effects and cognitive impairment among children.[19] The glial proliferation that accompanies lead encephalopathy[20] suggests a promoting effect.

As already described in other settings,[21] brain cancer risk was significantly elevated in the higher SES categories. When resulting from analyses of death certificates, such excess may be artifactual, due to better access to more accurate diagnostic procedures in higher social classes.[21] Nonetheless, in an analysis of occupational brain cancer risk based on the same data set as that in the present study, brain cancer risk was still elevated in intellectual, clerical, financial, commercial, and health-related occupations after adjustment by SES.[22] Because we controlled for social class in our analysis, we are confident that the

associations we observed with lead exposure were independent of either diagnostic bias or etiologic factors that might be associated with social class.

Limitations in our study do not allow definite conclusions. A major limitation derives from the use of the occupation and industry listed in the death certificate, as they represent only a fraction of the work history in a subject. These disadvantages are more important in studies involving women, as the reliability of the occupational information in the death certificate is poorer for women than men.[23] However, the resulting nondifferential misclassification would not overestimate risk at high-exposure categories,[24] but it would most likely underestimate it. This might account for the lower risk estimates in the present study, compared with the study in which exposure assessment was based upon blood lead measurements.[1] The use of death certificates provides only limited possibility to control for confounding or effect modification by lifestyle factors or other occupational exposures. We adjusted for marital status, residence, and SES in the analysis to reduce the effect of diagnostic bias and/or lifestyle factors on our results. Additional analyses adjusted for exposure to EMF, solvents, and metal dust. On the other hand, a main advantage in this study was the very large population size. This provides an ideal setting to generate hypotheses, which may be subsequently explored in more detail with analytical studies.

Poor detail in the occupation and industry coding system and incompleteness in working histories of study subjects are two critical factors for the performance of job-exposure matrices in identifying the exposure of interest,[25] and the 1980 Census three-digit occupation and industry codes may have not been specific enough in highlighting lead exposure. This would probably result in a diminished capacity to detect elevated risks. Indeed, only typesetters and compositors in the printing industry were associated with high-probability and high-level exposure to lead and the excess risk among Caucasians was entirely driven by this occupation. We explored brain cancer risk in the printing industry in detail, which overall was associated with a 30% risk increase (OR = 1.3; 95% CI = 1.1–1.5).[26] Among the various occupations in the printing industry, typesetters had the second greatest increase in brain cancer risk. Risk was highest among undefined manual occupations, including production helpers; machine feeders and offbearers; laborers; and occupation not reported (OR = 3.5; 95% CI = 1.9–6.4). Among African-American men, the excess was in the low probability of exposure, and too few subjects had medium or high probability of exposure. They were mainly laborers and operators of various machine types in the chemical, metal, and machinery manufacturing. The respective codes include numerous industries, with lead exposure occurring only in a few. Therefore, owing to the poor specificity of the coding system, they were classified as associated with low probability of exposure to lead.

In conclusion, evidence from epidemiological, experimental, and toxicologic studies suggests that lead exposure may be associated with brain cancer. Analytic studies of lead workers and lead-exposed populations with well-defined exposure and adequate statistical power to detect the association are urged in order to test the hypothesis.

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It Doesn't Always Pay To Be Smart

René Descartes: Appointed tutor of Queen Christina of Sweden, who orders him to write a ballet in verse and a comedy in five acts and to rise at 5 AM to teach philosophy. Catches a chill and dies of pneumonia.

Galileo Galilei: Empirically confirms that the earth moves around the sun. Is forced to recant and sentenced to house arrest.

Theodore Kaszynski: Math professor believes civilization has gone haywire. Writes unsigned article about it. Brother reads it. Thinks, "Sounds like Ted."

Lani Guinier, Robert Bork: Both write provocative articles that elevate their reputations. Both get nominated to high positions. Then, sadly, their enemies read the articles.

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